ASSESSMENT OF BAROREFLEX CONTRIBUTION TO SPONTANEOUS BLOOD PRESSURE-HEART RATE COUPLING BY CROSS MUTUAL INFORMATION

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Abstract- **A novel procedure is proposed to 1) quantify the level of physiological coupling existing between arterial blood pressure and heart rate variability during spontaneous behavior and 2) identify the relative contribution of the arterial baroreflex in the production of this coupling. The procedure is based on the estimation of the Cross-Mutual Information (CMI) between systolic blood pressure (SBP) and pulse interval (PI, the reciprocal of heart rate) beat-to-beat values. Use of this statistical function provides a quantification of both linear and nonlinear components of the coupling between variables. The procedure has been preliminarily applied to data collected in two spontaneously behaving cats before and seven days after the opening of the baroreflex loop. This allowed us to determine the baseline level of the SBP-PI coupling in intact conditions and the remaining fraction of SBP-PI coupling surviving deactivation of the baroreflex control function.**

We observed that in intact animals the cumulative physiological level of linear and nonlinear coupling between SBP and PI corresponded to 50% and 35%, respectively, of the theoretical maximal coupling. After removal of the baroreflex influence CMI values drastically dropped with respect to the above baseline values (-76% and –67%, respectively).

Thus, use of CMI indicates that the arterial baroreflex is the major determinant of the SBP-PI link, accounting for about 2/3 of the total measured coupling existing between these variables.

Keywords – **Nonlinearity, baroreflex, blood pressure variability, neural control, cardiovascular regulation**

I. INTRODUCTION

Arterial baroreflex is one of the most powerful mechanisms aimed at maintaining the blood pressure, BP, homeostasis. Any dysfunction in this control system usually results in a major BP lability with a consequent increased risk of adverse events for the patient [1]. For its crucial role in BP homeostasis, there is now an increasing demand for techniques able to quantify the dynamic characteristics of spontaneous baroreflex in a non invasive way and, possibly, during daily life.

Arterial baroreflex controls BP by driving several cardiovascular variables, including vascular resistance, heart contractility and heart rate, HR. Among other actions, the arterial baroreflex responds to BP perturbations by inducing opposite changes in HR thus being responsible for a certain level of coupling between these variables. Most of the techniques so far proposed for the analysis of spontaneous baroreflex function selectively focus on *linear* aspects of the BP-HR coupling [2]. In the present paper we propose a procedure able to quantify both *linear and nonlinear* components of the BP-HR coupling. This procedure has been used to 1) quantify the physiological level of coupling existing between BP and HR variability and 2) identify the relative contribution of baroreflex in the production of this coupling. This was done by developing a novel signal processing procedure based on mutual information and by applying this procedure on data collected in cats before and after the opening of the baroreflex loop.

II. METHODOLOGY

A. Mutual information

DEFINITION – Mutual information I(ξ,η) describes the amount of information on a given random quantity η we can obtain from the observation of another quantity ξ. When applied to a pair of signals [ξ(t),η(t)] mutual information provides a quantification of the coupling between these signals. It should be emphasized that, in contrast to many other techniques so far used for investigating cardiovascular variables, CMIF quantifies both linear and non-linear dependencies between signals. Moreover, being a pure statistical approach, it does not require any a-priori assumption on the nature of the signals, apart from the general assumption of ergodicity.

The concept of mutual information goes back to Shannon [3] and was originally applied to quantify information transmission over noisy channels. It is based on Shannon's entropy

$$H(x) = -\sum_m p_m \log_2 p_m \tag{1}$$

for a discrete distribution $\{p_m\}$ of any random variable ξ.

Mutual information is defined by:

$$I(x,h) \equiv H(h) - [H((x,h)) - H(x)] \tag{2}$$

where $H(h)$ represents the a-priori-uncertainty with regard to h, and $H((x,h)) - H(x)$ is the remaining a-posterior-uncertainty with regard to h if x is known.

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Abstract

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In our case, where two different signals ξ(t) and η(t+τ) are involved, I([ξ(t),η(t+τ)]) estimated for different values of τ is called *cross mutual information function, CMIF(τ).* For any given time lag t, CMIF may assume values determined by the following relation:

$$0 \leq \mathrm{CMIF}(t) \leq -\log_2 e \qquad (3)$$

where e is the relative measuring precision of the signals (0.25 in our case) and it is related to the partitioning of the amplitude range of each signal in bins. CMIF(τ) attains the lower bound of (3) only if there are no statistical dependencies between ξ(t) and η(t+τ)], namely in case of no coupling between signals. In case CMIF(τ) = - $\log_2$ *0.25*= 2 bit we can conclude that η(t+τ) is predictable from ξ(t), within precision e, this corresponds to a very strong coupling between variables.

SCHEME OF THE PROCEDURE – In the present paper we used CMIF to quantify the linear and nonlinear cross-dependencies between systolic, S(BP), and pulse interval (PI, the reciprocal of heart rate) as a function of the time lag τ. Thus we estimated CMIF from (3) by defining the vector *x(t)=[SBP(t); SBP(t-d)]* and the scalar *h*(t+τ)=*PI*(t+τ). The vector ***x(t)*,** which includes *SPB(t)* and *SBP(t-1)*, is used to predict *PI(t+t)*. The estimations were based on a ranking of the SBP and PI values so to obtain a more efficient computation and a reduced sensitivity to noise and outliers [4,5,6]. Moreover, since the ultimate scope of the procedure was to get an insight into the baroreflex control, we had to verify the baroreflex nature of the coupling quantified by CMIF. This was done by evaluating the results obtained in the cats before and after the opening of the baroreflex loop.

Essential information conveyed in each CMIF was also condensed by estimating the maximal value of CMIF (CMIF-max).

B. Data collection and processing

In two cats arterial blood pressure was intra-arterially recorded twice, before and seven days after the surgical opening of the baroreflex loop as obtained by a sino-aortic denervation (SAD). During the recordings, each lasting three hours, the cats were free to move within a large plexiglass box [7]. Each BP tracing was sampled at 200Hz and purified from artifacts by an interactive procedure. From each pressure waveform SBP and PI were identified, PI being the time interval between consecutive systolic peaks. Each SBP and PI series has been detrended, edited from outliers and split into 11 contiguous data segments each including 2048 beats (Fig.1). CMIF was then estimated for each data segment, after transformation of the original data into a ranked data set. Details of the procedure for CMIF estimation have been provided elsewhere [4,5].

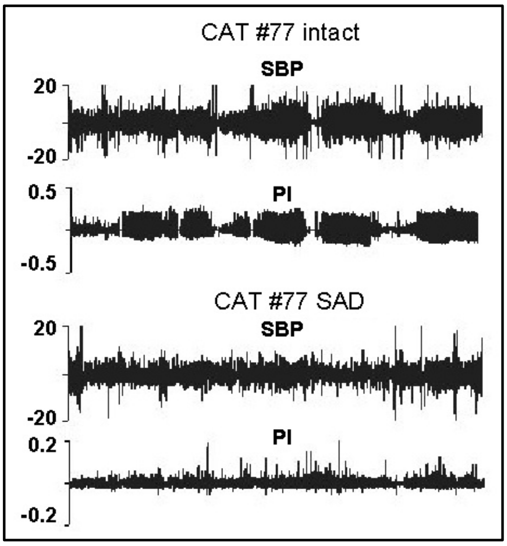

Fig 1 - Example of detrended data for cat #77 before (upper panels) and after SAD (lower panels).

III. RESULTS

Fig. 2 shows the cumulative CMIF plots estimated for the 11 consecutive data windows in animal #77 and #88 before and after SAD. In intact condition the average coupling level is about 50 % of the possible maximal value for cat #77 and about 35% for cat #88. It is worth noting that CMIF values are not fixed but rather fluctuate over time, possibly reflecting the different activity of the animals during spontaneous behavior. After denervation CMIF values underwent a major reduction.

These trends are confirmed in table 1 where the average values of the CMIF-max, i.e. the maximum value of each CMIF curve, are reported for both the animals in the intact and denervated condition. The marked reduction in the CMIF curves observed in Fig.2, is here confirmed by the dramatic fall in the CMIF-max values after SAD (-76% and –67%, respectively) with respect to intact condition.

TABLE I
CMIF-max VALUES OVER THE 11 DATA SEGMENTS
Data are expressed as MEAN (SD)

	Cat #77		Cat #88	
	intact	SAD	Intact	SAD
CMIF-max	1.00 (0.25)	0.25 (0.12)	0.69 (0.19)	0.22 (0.07)

Time-modulation of CMIF-max over time is represented in Fig.3. Here the CMIF-max values progressively obtained from the analysis of the consecutive data segments are shown.

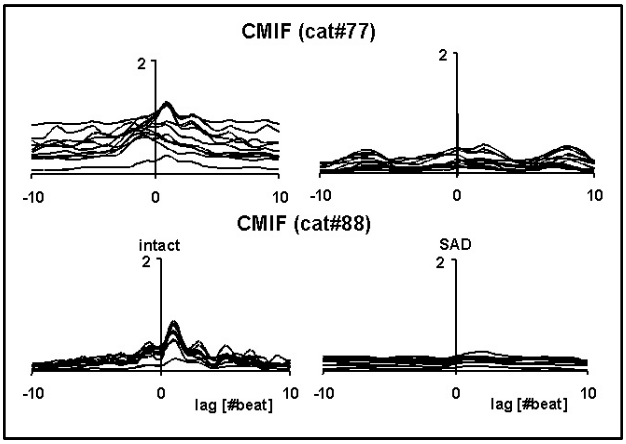

Fig. 2 - Cumulative plots of Cross-Mutual Information Function (CMIF) estimated over the 11 data segments for cats #77 and cat #88 before and after SAD

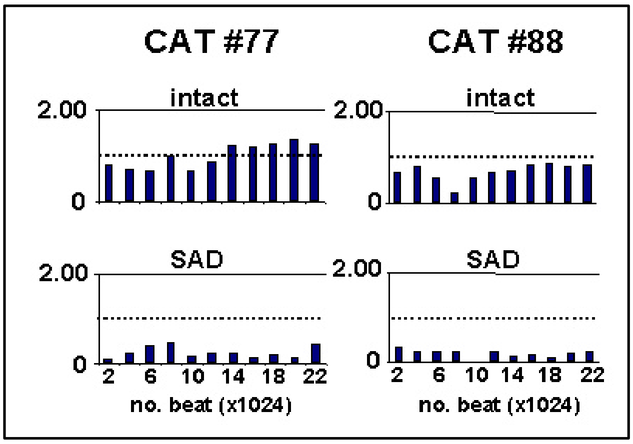

Fig.3 Time course of CMIF-max for cat #77 and #88. Data are shown as a function of the progressive data segment including 2048 beats.

IV. DISCUSSION

Application of mutual information allowed us to obtain a comprehensive quantification of the physiological coupling existing between blood pressure and cardiac rhythm during spontaneous behavior, including any possible linear and nonlinear component of such a coupling. Obviously, the presence of interactions between SBP and PI is not surprising *per se* and a number of quantifications of specific aspects of this interaction have already being obtained through linear techniques [2].

The specific feature of the proposed technique is the wider perspective from which this phenomenon can be evaluated, which allows for the first time to obtain the overall quantification of all aspects of SBP-PI coupling, including non-linear components. These non-linear components have been suggested to represent an important fraction of the fluctuations in cardiovascular parameters but, for technical reasons, have been so far left largely unexplored. The findings stemming from this analysis clearly indicates that the arterial baroreflex plays a major role in the overall link between SBP and PI, and that its buffering action accounts for more than 2/3 of the total measured coupling existing between these cardiovascular variables.

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